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Blood Coagulation & Fibrinolysis

Perioperative Laboratory Monitoring in Congenital Haemophilia Patients with Inhibitors: A Systematic Literature Review

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	reporting perioperative laboratory monitoring in patients with congenital haemophilia A or B, resulting in 24 articles undergoing data extraction. Routine perioperative assay monitoring practices were the most commonly reported (n=20/24); thrombin generation assay (TGA) was the least commonly reported (n=2/24). Other monitoring practices described were factor VII and factor VIII coagulation activity (FVII:C, FVIII:C) (n=8/24, n=5/24, respectively), and thromboelastography (TEG) or rotational thromboelastometry (ROTEM) assessments (n=3/24). The impact of monitoring on treatment decisions was, however, rarely reported. In conclusion, many methods of perioperative monitoring of haemophilia patients with inhibitors have been identified in this review, yet there is a lack of reporting in larger scale cohort studies. More detailed reporting on the impact of monitoring outcomes on treatment decisions is also needed to share best practice, particularly as new therapeutic agents emerge.

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Perioperative Laboratory Monitoring in Congenital Haemophilia Patients with Inhibitors: A Systematic Literature Review

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Abstract

Although the use of clotting factor concentrates is the mainstay of haemophilia care, the development of inhibitors complicates disease management. Perioperative management of patients with inhibitors is therefore a challenge. A systematic literature review was performed to identify literature reporting on the perioperative monitoring and management of haemophilia. MEDLINE, Embase and Cochrane databases were searched from database inception to 26 March 2018. Recent congress proceedings were also searched. Titles and abstracts, then full texts, were screened for relevance by two reviewers. Quality of included studies was assessed using the Critical Appraisal Skills Programme checklist. Of the 2,033 individual entries identified, 86 articles met the inclusion criteria. The identified studies were screened again to find papers reporting perioperative laboratory monitoring in patients with congenital haemophilia A or B, resulting in 24 articles undergoing data extraction. Routine perioperative assay monitoring practices were the most commonly reported (n=20/24); thrombin generation assay (TGA) was the least commonly reported (n=2/24). Other monitoring practices described were factor VII and factor VIII coagulation activity (FVII:C, FVIII:C) (n=8/24, n=5/24, respectively), and thromboelastography (TEG) or rotational thromboelastometry (ROTEM) assessments (n=3/24). The impact of monitoring on treatment decisions was, however, rarely reported. In conclusion, many methods of perioperative monitoring of haemophilia patients with inhibitors have been identified in this review, yet there is a lack of reporting in larger scale cohort studies. More detailed reporting on the impact of monitoring outcomes on treatment decisions is also needed to share best practice, particularly as new therapeutic agents emerge.

Key words: Haemophilia; Surgery; Inhibitors; Laboratory Monitoring; Systematic Literature Review

INTRODUCTION

Haemophilia is a rare disease caused by a deficiency of coagulation factor VIII (FVIII) (haemophilia A, HA) or factor IX (FIX) (haemophilia B, HB) and leaves patients more prone to excessive bleeding.[1] The standard of care for severe haemophilia (factor activity <1 IU/dl), and some patients with moderate haemophilia (factor activity 1-5 IU/dl), is to prevent or minimise bleeding episodes using infusions of the missing factor concentrate (prophylaxis). Breakthrough bleeds may still occur requiring additional on-demand treatment. Treatment protocols, intensity of prophylaxis or choice to remain on-demand alone must be tailored to individual needs together with consideration of the local health economics.[1]

In response to regular treatment, a subgroup of haemophilia patients of all severities can produce immunoglobulin G (IgG) antibodies, termed 'inhibitors', which work to neutralise clotting factors.[2, 3] Inhibitors complicate prophylaxis and on-demand management by reducing or fully neutralising the efficacy of infused factor concentrates, depending on the detected inhibitor titre.[1, 4]

Persistent inhibitors are a concern for haemophilia patients, particularly if undergoing surgical procedures.[5] Permanent tolerance induction in severe haemophilia (immune tolerance induction, ITI) is the preferable strategy to minimise future bleeding and/or management risks of surgery in the presence of an inhibitor.[6, 7] Tolerising practices may also include the use of anti-CD20 monoclonal antibody, immunoadsorption and plasmapheresis for additional short-term benefit.[5] Strategies for re-achieving tolerance in non-severe HA are less well defined.[8]

Knowledge of previous and/or current inhibitor status prior to surgery is crucial, either as repeat laboratory assessment ahead of surgery if time allows (severe haemophilia), reference to laboratory screening since the most recent FVIII concentrate exposure (non-severe HA), or attention to *in vivo* recovery and perioperative efficacy of infused concentrate (all severities) during the peri- and post-surgical course.[6, 9]

The monitoring and management of haemophilia patients with inhibitors undergoing surgical procedures is a particular challenge, and is the focus of this review.

MATERIALS AND METHODS

Search Strategy for Identification of Studies

A systematic literature review was performed in accordance with a pre-specified search protocol designed to identify literature reporting on the perioperative monitoring and management of haemophilia patients with inhibitors. The review process involved searching electronic databases, and hand-searching of key haemophilia/haematology conference proceedings from the last two years and reference lists of any relevant systematic reviews identified during the searches.

All electronic databases were searched on 26 March 2018. The databases searched to identify relevant published literature were: MEDLINE, MEDLINE In-Process, MEDLINE Daily and MEDLINE Epub Ahead of Print (1946 to present); Embase (1974 to 23 March 2018); The Cochrane Database of Systematic Reviews (CDSR): Issue 3 of 12, March 2018; The Database of Abstracts of Reviews of Effects (DARE): Issue 2 of 4, April 2015; The Cochrane Central Register of Controlled Trials (CENTRAL): Issue 2 of 12, February 2018.

In addition to the electronic database searches, hand-searches were performed to generate further evidence from a variety of sources. The bibliographies of published systematic reviews identified through the electronic database searches were hand-searched to identify any additional relevant studies for inclusion in the review. The proceedings of relevant haemophilia and haematology congresses that had taken place within approximately two and a half years prior to December 2017 were also hand-searched, including: American Society of Hematology Annual Meeting (2015, 2016, 2017); British Society for Haematology Annual Scientific Meeting (2016, 2017); European Association for Haemophilia and Allied Disorders Annual Congress (2016, 2017); Haemophilia and Thrombosis Research Society Scientific Symposium (2015, 2017); European Hematology Association (EHA) Congress (2016, 2017); International Society for Thrombosis and Haemostasis Congress (2016, 2017); World Federation of Hemophilia (WFH) World Congress (2016). The websites and abstract books of these congresses were searched, if available, using terms based on the complete list of electronic database search terms.

Full details of the search strategies for the electronic database searches and the congress searches are presented in Supplementary Table 1–3.

Study Selection

All articles retrieved through the electronic database searches and hand-searches were screened by two independent reviewers and included based on their alignment with the predefined eligibility criteria (Supplementary Table 4). The strategy was specifically designed to capture studies reporting on the monitoring and/or management of haemophilia patients with inhibitors undergoing surgery. All articles were initially screened based on their abstracts only. Following the abstract review stage, the full texts of remaining articles were then screened for relevance to produce the final list of included studies. For pragmatic reasons, additional study design eligibility criteria were applied during the screening of full texts to ensure that only interventional and observational studies were included in the final list. Study designs were determined by their description as reported by authors in the papers. In cases where the study design was not explicitly stated, the reviewers defined observational studies as those that examined and analysed the data of a patient cohort as a group, compared to an analysis of individual patient data only in case series. Studies that described patients being assigned to a specific treatment group were categorised as interventional. A full list of papers excluded, and the reasons for their exclusion, at the full text screening stages of the review is shown in Supplementary Table 5. In addition, a list of the case studies identified during the review and excluded based on study design prior to full text screening is available in Supplementary Table 6.

Data Extraction and Analysis

Following application of the eligibility criteria, there was still a large number of included studies. Therefore, the list was screened an additional time by one reviewer, and checked by a second reviewer, to identify the studies that reported perioperative laboratory monitoring in patients with congenital HA or HB. In cases of studies reporting on both congenital and acquired haemophilia patients, only information on congenital patients was extracted. Data were extracted from each article by a single individual, and reviewed by a second.

Since included studies are of different designs, their quality was assessed using the Critical Appraisal Skills Programme (CASP) checklist most appropriate for the study design (e.g. case control study, cohort study, randomised controlled trial).

RESULTS

Search Results

The literature search retrieved 1,481 abstracts from electronic databases, 502 abstracts from conference proceedings and 50 articles from hand searches of existing review bibliographies. Following application of the eligibility criteria to the identified abstracts and, subsequently, full text articles (Figure 1), a final list of 86 relevant articles was identified (Table 1).

In the interest of focusing the review more specifically, the 86 full text articles were screened once more to identify the studies reporting perioperative laboratory monitoring in patients with congenital HA or HB and inhibitors. This resulted in a final list of 24 articles that underwent full data extraction (Table 2).

Quality Assessment

Quality assessments were carried out for the interventional and observational studies that underwent data extraction (Supplementary Table 7–8). Overall, the issues addressed by the interventional studies were clearly focused and all patients were properly accounted for. The most substantial limitation of the interventional studies was a lack of blinding (8/9 studies), which may have led to bias in the ascertainment and reporting of outcomes. For the observational studies, follow-up was almost always complete (14/15) but due to a lack of reporting, many of the quality assessment questions had to be marked as not applicable.

Perioperative Monitoring

Overall, 40% (34/86) of articles identified through the review mentioned how patients were monitored; of these, nearly three quarters (24) of the articles mentioned the use of laboratory monitoring in patients with inhibitors complicating congenital HA or HB, either in the methods section or when describing the outcomes of the study (Table 1). However, even in studies which mentioned laboratory monitoring, the use and impact of specific monitoring protocols on treatment decisions was often not well described. Instead, it was common for the details of perioperative monitoring to be provided for information only, or to report the haemostatic efficacy of the treatment.

Routine laboratory monitoring

Amongst the studies reporting perioperative laboratory monitoring practices, routine laboratory monitoring practices, such as platelet count, prothrombin time (PT), activated partial thromboplastin time (APTT), fibrinogen levels, D-dimer levels and antithrombin (ATIII) were the most commonly reported. This monitoring information was frequently provided to demonstrate efficacy, or lack thereof, and determine safety, of the haemostatic agent, particularly in the context of interventional studies.[10, 11] In the majority of studies it was unclear whether the outcomes of laboratory tests were available to the care team within the timeframe necessary to influence treatment decisions (Table 3).[12, 13]

When the influence of monitoring on clinical decisions was discussed, this was mainly in the context of individual patient cases, such as reduction in activated prothrombin complex concentrate (aPCC) treatment following elevation in D-dimer levels,[14] as opposed to providing insight into how laboratory monitoring influenced treatment decisions and outcomes on a cohort-wide level. In other cases, laboratory tests were only utilised in patients who experienced an adverse event.[15]

Overall, very limited information was found in the identified studies to indicate the influence of perioperative monitoring results on clinical decisions.

Factor VII

A total of 8 of the 17 extracted studies describing treatment with recombinant factor VIIa (rFVIIa), administered continually (CI) or using bolus doses, described the monitoring of factor VII coagulation activity (FVII:C) (Table 4). Two studies published by the same centre described monitoring FVIIa levels using a one-stage coagulation assay suggesting that coagulation activity as opposed to protein levels was assessed. The studies from this centre also report that the specific FVIIa assay (Staclot™, Diagnostica Stago) was not found to be practical or reliable.[16, 17]

Even where FVII:C monitoring is mentioned, FVII:C was rarely used to make dosing decisions. In one study investigating continuous infusion of rFVIIa, observed bleeding was used to deduce that the target FVII:C of 10 IU/dl was insufficient.[18] Two other studies noted that in patients with ineffective haemostatic efficacy, FVII:C often exceeded the target 30 IU/ml.[10, 19]

When comparing CI to bolus administration, one study found that FVII:C levels were consistently higher in patients undergoing CI; however, the difference was not statistically significant, and there was no difference in haemostatic efficacy between groups (75% vs. 73%, respectively).[19]

Thromboelastography/Rotational thromboelastography analysis

Thromboelastography (TEG) or rotational thromboelastography (ROTEM) coagulation assessments were used in three of the more recent studies assessing a variety of agents (including rFVIIa, aPCC, and FVIII) (Table 5). In one study, ROTEM analysis on *in vitro* samples was used to identify the minimum necessary dose of activated coagulation products and most suitable treatment (rFVIIa vs. aPCC) for perioperative haemostatic control in patients with inhibitors.[20] This study found that preoperative *in vitro* ROTEM analysis more accurately predicted the impact of treatment with rFVIIa than with aPCC.[20] The other studies used ROTEM intraoperatively to demonstrate haemostatic efficacy, but did not report how the outcomes impacted clinical treatment decisions.[21, 22]

Factor VIII:C

Four studies were found to have analysed human FVIII:C, while one analysed porcine FVIII:C (Table 6).[13, 21-24] The use of FVIII:C to identify cases of 'resistance' to porcine FVIII concentrate was discussed in an early study,[13] however, only one recent study mentioned how FVIII:C monitoring influenced treatment decisions.[24] This retrospective observational study involved routine monitoring of FVIII:C and when one patient's FVIII:C levels declined after a total knee replacement, their treatment was switched from cryoprecipitate to plasma-derived FVIII (pdFVIII), leading to a good haemostatic outcome.[24]

Thrombin generation

Only two articles described monitoring using a thrombin generation assay (TGA) (Table 7).[22, 25] In one of these studies, TGA parameters were used to assess haemostatic efficacy, with no indication of how the results impacted care decisions.[22] The other, a 2016 study involving 10 inhibitor patients undergoing orthopaedic surgery, investigated the association between TGA and clinical bleeding events, finding that there was no difference in the TGA values between patients who did and did not experience bleeding complications.[25]

DISCUSSION

Whilst this review uncovered evidence on the methods of monitoring and management used in haemophilia patients undergoing surgery, there was very little information to indicate how the outcomes of laboratory monitoring practices were used to influence treatment decisions. In papers where the impact of monitoring was mentioned, this tended to be described on an individual patient basis. Therefore, it is difficult to use the available evidence to understand to what extent laboratory monitoring is used in clinical practice and how it could be utilised to improve patient care.

Another barrier to understanding the impact of perioperative monitoring in haemophilia patients is the lack of a generalisable assay for aPCC and rFVIIa. Monitoring of patients undergoing treatment with these agents is currently conducted according to local protocols, instead of a global standard, with centres forced to evaluate treatment efficacy through clinical, rather than laboratory, assessments.

In addition, while some evidence related to monitoring and management with traditional treatments, such as rFVIIa, aPCC and FVIII was found, the review did not identify published literature reporting on such practices in patients treated with emerging therapeutics, such as emicizumab, concizumab and fitusiran. There are currently only anecdotal data about surgical haemostasis planning in patients with these agents on board.[26, 27] In such scenarios, monitoring for all these agents will be complex, both in terms of consideration of appropriate laboratory assays, together with interpreting results in the context of global haemostatic potential.

Emicizumab, a recombinant, humanised, bispecific monoclonal antibody recently approved for treatment of HA with inhibitors by the Food and Drug Administration (FDA), works by acting similarly to activated factor VIII in bridging activated factor IX and factor X to trigger the coagulation cascade.[28] As emicizumab affects intrinsic pathway clotting-based laboratory tests, including activated clotting time (ACT) and all assays based on APTT, intrinsic pathway clotting-based laboratory test results should not be used to monitor emicizumab activity, determine dosing for factor replacement or anti-coagulation, or measure FVIII inhibitor titres in patients receiving this treatment.[29] A recent case study describing the use of rescue aPCC treatment to provide additional haemostatic control during a spontaneous bleeding event in a patient receiving prophylactic emicizumab used TGA to determine the optimal aPCC dosage to maintain haemostatic efficacy while limiting the risk of thrombotic complications.[30] While this review identified an interventional study reporting the use of emicizumab in haemophilia patients with inhibitors undergoing surgery, no information on perioperative laboratory monitoring was provided.[27]

Concizumab, a humanized monoclonal antibody against tissue factor pathway inhibitor, is under investigation for the prophylactic treatment of HA and HB patients with inhibitors in a phase II trial due to complete in 2019 (NCT03196284).[31] Previous studies have used TGA to demonstrate concizumab activity, suggesting that this may be a potential method of evaluating efficacy in clinical practice.[32] Lastly, fitusiran, an investigational RNA interference therapy, works by targeting ATIII messenger RNA to suppress ATIII production.[33] One interventional study examining fitusiran treatment in haemophilia patients undergoing surgery was identified in this review, but no details on perioperative laboratory monitoring were reported.[34] As these emerging therapies enter the market it will be important to establish an understanding of the standard of care used to monitor patients receiving these treatments.

While data on these emerging therapies are currently limited it is difficult to predict response to treatment during surgery, as well as expectations from monitoring. Efforts have been made to standardise TGA, but these developments are rarely shared outside of research settings. More information is therefore needed to understand their use in patients with inhibitors undergoing surgery in clinical practice. As the availability of data on suitable assays remains limited, the United Kingdom Haemophilia Centres Doctors' Organisation has recommended that non-urgent major surgery in haemophilia patients with inhibitors receiving novel prophylaxis agents is delayed, until more specific methods of monitoring these patients can be found or treatment algorithms and risks are better understood.[35]

For pragmatic reasons, the scope of the review was limited to include only interventional and observational studies. The results of this review indicate that the currently available higher quality evidence base provides little insight into the standard of care for the use of laboratory monitoring in the management of haemophilia patients with inhibitors undergoing surgery. This topic has also been addressed in case studies and series, including a case series reported by Dargaud et al. in 2010.[36] This paper investigated the use of TGA in monitoring efficacy of agents in surgical procedures for six patients and showed that TGA results correlated with clinical bleeding risk and endogenous thrombin potential can be used to monitor agent efficacy in their hands.[36] These results were not supported by a later, larger scale study involving 10 inhibitor patients undergoing surgery identified by our review however, as no significant differences in TGA parameters between haemophilia patients with inhibitors who did and did not experience bleeding complications following surgery were found.[25] Whilst case studies and series can provide valuable insight, they are considered to be a source of lower quality evidence due to their risk of bias and potential lack of generalisability to a wider patient population. The results of this review, therefore, highlight the need to report higher quality evidence on monitoring and managing surgical haemophilia patients with inhibitors to establish a standard of care in this area.

CONCLUSION

In conclusion, this systematic literature review demonstrated that there are multiple methods of laboratory monitoring used in haemophilia patients with inhibitors undergoing surgery, although these are largely reported in the context of clinical trials looking to evaluate unforeseen complications of candidate haemostatic agents. Currently no generalisable assays exist for examining treatment efficacy against high titre inhibitors, and instead clinicians are forced to rely on empirical dosing and consensus guidance. With the introduction of novel agents, this landscape may be complicated further. Where data on monitoring of inhibitor treatment exist, there is little information from higher quality evidence sources to indicate how the outcomes of such practices are used to inform treatment decisions. There is a need to develop more robust evidence in this area to establish a standard of care for perioperatively monitoring haemophilia patients with inhibitors who are treated with current and emerging haemostatic therapies.

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Study conception/design and acquisition of data: DPH, CRMH, RL, GT, BDM, MM; analysis/interpretation of data: DPH, CRMH, RL, GT, BDM, MM; drafting of the publication, or revising it critically for important intellectual content: DPH, CRMH, RL, GT, BDM, MM; final approval of the publication: DPH, CRMH, RL, GT, BDM, MM.

CONFLICTS OF INTEREST/DISCLOSURES

DPH has received research support from Octapharma, Bayer and Shire, speaker and/or consultancy honoraria from Pfizer, Shire, Sobi, Biomarin, Uniqure, Roche, Octapharma, Novo Nordisk and Biotest; CRMH has attended advisory boards organised by Roche, received research support from Novo Nordisk, Pfizer, Shire, Bayer and Sobi, and acted as speaker in sponsored symposia for Pfizer, Shire, Bayer, Sobi and Biotest; RL has received speaker fees from Octapharma, BPL and Bayer, consultancy fees from Bayer, Octapharma, Novo Nordisk, Shire and Grifols, has attended an advisory board organised by Roche, and was an investigator for the HAVEN 2 study; GT is an employee of Roche Products Ltd.; BDM is an employee of Costello Medical; MM has provided consultancy to CSL Behring and Novo Nordisk and attended advisory boards organised by Shire and Bioverativ.

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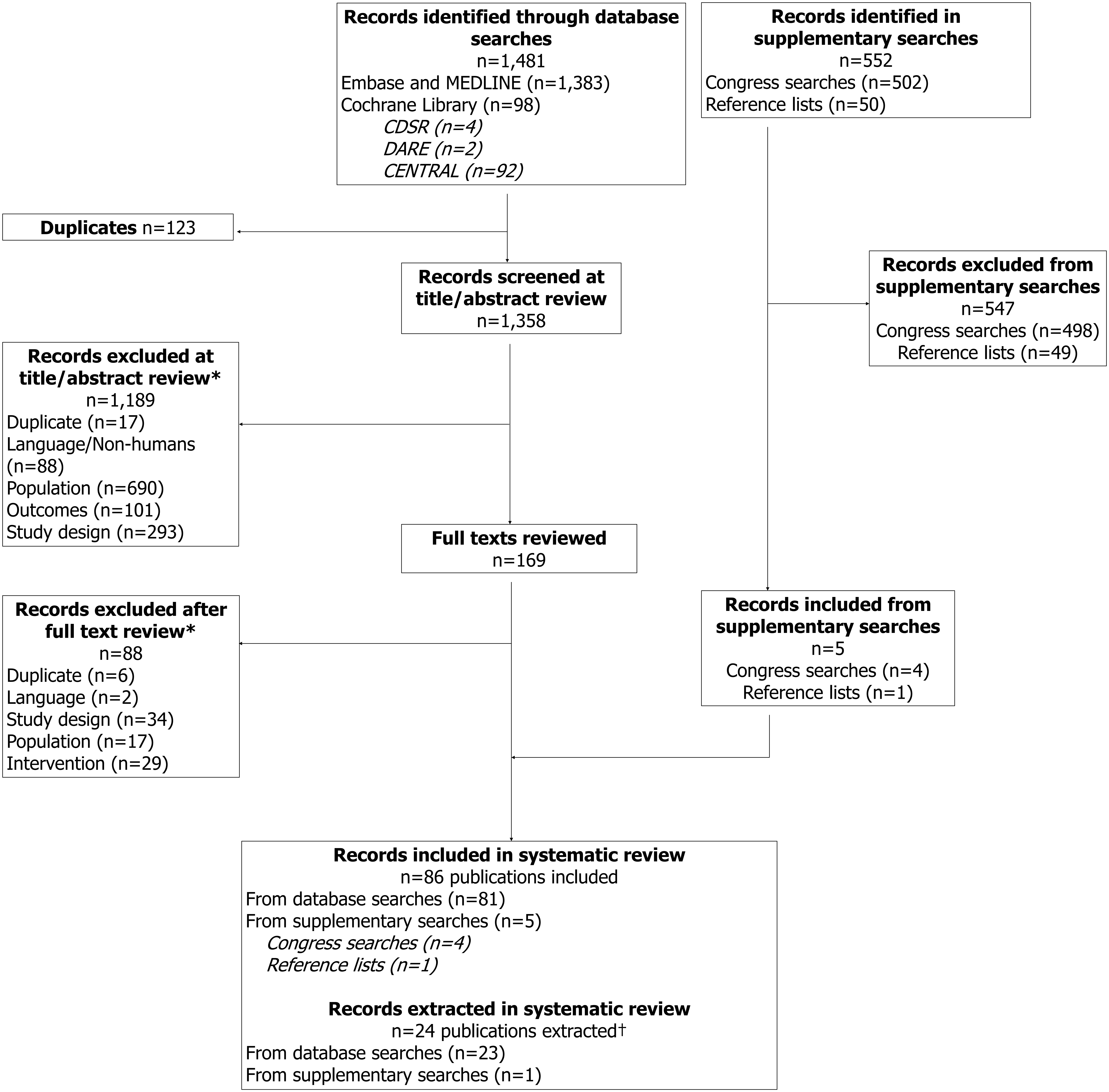
FIGURE LEDGEND

Figure 1. Systematic Review of Clinical Studies

[†]Only articles discussing laboratory monitoring were extracted

Figure 1



Records identified through database searches
n=1,481
Embase and MEDLINE (n=1,383)
Cochrane Library (n=98)
CDSR (n=4)
DARE (n=2)
CENTRAL (n=92)
Records identified in supplementary searches
n=552
Congress searches (n=502)
Reference lists (n=50)
Duplicates n=123
Records screened at title/abstract review
n=1,358
Records excluded from supplementary searches
n=547
Congress searches (n=498)
Reference lists (n=49)
Records excluded at title/abstract review*
n=1,189
Duplicate (n=17)
Language/Non-humans (n=88)
Population (n=690)
Outcomes (n=101)
Study design (n=293)
Full texts reviewed
n=169
Records excluded after full text review*
n=88
Duplicate (n=6)
Language (n=2)
Study design (n=34)
Population (n=17)
Intervention (n=29)
Records included from supplementary searches
n=5
Congress searches (n=4)
Reference lists (n=1)
Records included in systematic review
n=86 publications included
From database searches (n=81)
From supplementary searches (n=5)
Congress searches (n=4)
Reference lists (n=1)
Records extracted in systematic review
n=24 publications extracted†
From database searches (n=23)
From supplementary searches (n=1)

Table 1. Studies Included Following Full Text Screening

Study	Study Type	Country	Monitoring reported
Congenital haemophilia			
Alenda et al. 2016[37]	Observational	Spain	Not reported
Antmen et al. 2015[38]	Observational	Turkey	Not reported
Antmen et al. 2018[39]	Observational	Turkey	Not reported
Balkan et al. 2010[12]	Observational	Turkey	Laboratory monitoring
Bensadok et al. 2015[40]	Observational	Algeria	Not reported
Carulli et al. 2017[41]	Observational	Italy	Not reported
Caviglia et al. 2011[42]	Observational	Argentina	Not reported
Caviglia et al. 2016[43]	Observational	Argentina	Not reported
Chapin et al. 2017[44]	Observational	USA	Not reported
Ciavarella et al. 1984[45]	Interventional	Italy	Not reported
Danielson et al. 2017[24]	Observational	Finland	Laboratory monitoring
Dimichele et al. 2006[46]	Observational	USA and Europe	Not reported
Freiburghaus et al. 1998[47]	Observational	Sweden	Not reported
He et al. 2017[48]	Observational	China	Not reported
Holmström et al. 2012[22]	Interventional	Norway and Sweden	Laboratory monitoring
Ingerslev et al. 1996[49]	Observational	Multiple	Laboratory monitoring
Ingerslev et al. 2000[50]	Observational	Denmark	Not reported
Jenkins et al. 2013[51]	Observational	UK	Not reported
Karagun et al. 2016	Observational	Turkey	Not reported
Kitchens et al. 1986[52]	Observational	USA	Not reported
Kizilocak et al. 2016[53]	Observational	Turkey	Not reported
Kruse-Jarres et al. 2017[27]	Interventional	Multiple	Not reported
Lauroua et al. 2009[54]	Observational	France	Both [clinical and laboratory monitoring]
Lim et al. 2014[55]	Observational	USA	Not reported

Study	Study Type	Country	Monitoring reported
Lozier et al. 1993[56]	Observational	Multiple	Not reported
Ludlam et al. 2003[10]	Interventional	UK and Italy	Laboratory monitoring
Mahasandana et al. 1993[57]	Observational	Thailand	Not reported
Mancuso et al. 2008[58]	Observational	Italy	Not reported
Morado et al. 2001[59]	Observational	Spain	Not reported
Negrier et al. 2018[34]	Interventional	Multiple	Not reported
Nguyen et al. 2018[60]	Observational	Vietnam	Not reported
Nilsson et al. 1977[61]	Observational	Sweden	Laboratory monitoring†
O'Connell et al. 2002[62]	Observational	Ireland and UK	Clinical monitoring
Oldenburg et al. 2017[63]	Observational	Multiple	Not reported
Ozdemir et al. 2011[64]	Observational	Turkey	Not reported
Pruthi et al. 2007[19]	Interventional	USA	Laboratory monitoring
Quintana-Molina et al. 2004[65]	Observational	Spain	Laboratory monitoring
Rodriguez-Merchan et al. 2007[66]	Observational	Spain	Not reported
Rodriguez-Merchan et al. 2010[67]	Observational	Spain	Not reported
Sasmaz et al. 2012[68]	Observational	Turkey	Not reported
Sasmaz et al. 2015[69]	Observational	Turkey	Not reported
Sasmaz et al. 2018[70]	Observational	Turkey	Not reported
Szczepanik et al. 2018[71]	Observational	Poland	Not reported
Serban et al. 2009[72]	Observational	Romania	Not reported
Shapiro et al. 1998[73]	Interventional	USA	Laboratory monitoring
Shapiro et al. 2012[74]	Observational	USA	Not reported
Smith et al. 2002[75]	Observational	Ireland and UK	Both [clinical and laboratory monitoring]

Study	Study Type	Country	Monitoring reported
Solimeno et al. 2009[76]	Observational	Italy	Not reported
Takedani et al. 2010[77]	Observational	Japan	Not reported
Acquired haemophilia			
Gringeri et al. 2011[78]	Observational	Europe	Laboratory monitoring
Lak et al. 2010[79]	Observational	Iran	Laboratory monitoring
Liozon et al. 1997[80]	Observational	France	Laboratory monitoring
Ma et al. 2016[81]	Interventional	USA	Not reported
Novack et al. 2015[82]	Observational	Multiple	Not reported
Both congenital and acquired haemophilia			
Atalar et al. 2016[83]	Observational	Turkey	Not reported
Boadas et al. 2011[84]	Observational	Venezuela	Both [clinical and laboratory monitoring]‡
Carulli et al. 2016[85]	Observational	Italy	Not reported
Castaman et al. 2015[86]	Observational	Italy	Not reported
Croteau et al. 2016[87]	Interventional	USA	Not reported
Furukawa et al. 2015[20]	Interventional	Japan	Laboratory monitoring
Gatti et al. 1984[13]	Interventional	Italy	Laboratory monitoring
Habermann et al. 2004[23]	Observational	Germany	Laboratory monitoring
Hilgartner et al. 1983[88]	Observational	USA	Not reported
Ju et al. 2015[89]	Observational	South Korea	Clinical monitoring
Kavakli et al. 2012[90]	Observational	Turkey	Not reported
Kraut et al. 2007[14]	Observational	USA	Laboratory monitoring
Linari et al. 2015[91]	Observational	Italy	Not reported
Mancuso et al. 2016[25]	Observational	Italy	Laboratory monitoring
Mauser-Bunschoten et al. 1998[16]	Observational	Netherlands and Belgium	Both [clinical and laboratory monitoring]
Mauser-Bunschoten et al. 2002[17]	Observational	Netherlands	Both [clinical and laboratory monitoring]
Negrier et al. 1997[92]	Observational	France	Not reported

Study	Study Type	Country	Monitoring reported
Negrier et al. 2013[93]	Observational	Worldwide: Colombia, France, Germany, Italy, South Korea, Sweden and the UK	Both [clinical and laboratory monitoring]
Polyanskaya et al. 2012[94]	Observational	Russia	Clinical monitoring
Rangarajan et al. 2011[95]	Observational	UK	Clinical monitoring
Rodriguez-Merchan et al. 2004[96]	Observational	Worldwide	Not reported
Rodriguez-Merchan et al. 2007[66]	Observational	Spain	Not reported
Santagostino et al. 2001[97]	Observational	Italy	Laboratory monitoring
Sasmaz et al. 2015[98]	Observational	Turkey	Not reported
Scharf et al. 1996[99]	Observational	Poland	Not reported
Scharrer et al. 1999[15]	Interventional	Germany	Both [clinical and laboratory monitoring]
Serban et al. 2014[21]	Observational	Romania	Both [clinical and laboratory monitoring]
Smith et al. 2001[18]	Interventional	Unclear	Both [clinical and laboratory monitoring]
Szczepanik et al. 2009[71]	Observational	Poland	Not reported
Takedani et al. 2015[77]	Observational	Japan	Clinical monitoring
Tjonnfjord et al. 2004/ Tjonnfjord et al. 2006[100, 101]	Observational	Norway	Laboratory monitoring

†Outcomes not reported separately for inhibitor patients so data not extracted; ‡No monitoring results reported so data not extracted

Table 2

Table 2. Overview of Studies Reporting Perioperative Laboratory Monitoring

Study	Study design	Patients	Procedures	Haemostatic treatment	Haemostatic outcome
Balkan C et al. 2010[12]	Single-centre, retrospective observational study	30 HA patients with high responding inhibitors	11 major 42 minor	• aPCC, or • rFVIIa, or • Sequential use of aPCC and rFVIIa	• aPCC: 22/22 (100%) bleeding controlled • rFVIIa: 31/33 (94%) bleeding controlled
Danielson H et al. 2017[24]	Single-centre, retrospective observational study	6 HA patients with inhibitors (n=2 low-responding, n=4 high-responding)	15 orthopaedic	• Cryoprecipitate, or • Coagulation FVIII (pdFVIII or rFVIII), or • aPCC, or • rFVIIa (post-treatment switch in some individual cases)	8/15 (53%) bleeding controlled (rated as 'good', indicating no difference in bleeding compared to normal arthroplasty)
Furukawa S et al. 2015[20]	Single-centre, prospective interventional study	8 HA patients with inhibitors	8 elective	• rFVIIa, or • aPCC	8/8 (100%) bleeding controlled
Gatti L et al. 1984[13]	Single-centre, prospective, uncontrolled interventional study	5 HA patients with inhibitors	3 minor 2 major	• Bolus porcine FVIII (Hyate:C) (minor dental), or • Continuous porcine FVIII (Hyate:C) (major)	2/2 (100%) bleeding controlled (only reported for major surgery)
Habermann B et al. 2004[23]	Single-centre, retrospective observational study	4 HA patients with inhibitors	6 orthopaedic	Anvitoff™ (containing TXA) in combination with: • bolus FVIII (low inhibitor titre) • immunoabsorbant therapy (Therasorb™) followed by bolus FVIII (high inhibitor titre) • continuous rFVIIa infusion when inhibitor titres rose/could not be eliminated or FVIII response decreased	5/6 (83%) bleeding controlled
Holmström M et al. 2012[22]	Two-centre, prospective interventional study	6 HA patients with high responding inhibitors	2 minor 5 major	Bolus aPCC in combination with TXA	6/7 (86%) bleeding controlled

Study	Study design	Patients	Procedures	Haemostatic treatment	Haemostatic outcome
Ingerslev J. et al. 1996[49]	Multicentre, retrospective observational study	11 HA patients and 1 HB patient with inhibitors	13 major	Bolus rFVIIa	12/12 (100%) bleeding controlled (Outcome not reported in n=1 case)
Kraut EH et al. 2007[14]	Multicentre, retrospective chart review	6 HA patients with inhibitors	21 various	• Bolus aPCC monotherapy, or • Bolus rFVIIa monotherapy, or • Bolus/continuous combination therapy	14/21 (67%) bleeding controlled
Lauroua P et al. 2009[54]	Single-centre, retrospective observational study	7 HA patients with inhibitors	8 major elective 2 major emergency 2 minor elective	Bolus aPCC as first-line treatment	Haemostatic outcomes were consistent with non-coagulopathic patients undergoing similar procedures
Ludlam A et al. 2003[10]	Prospective, interventional study	9 HA patients with inhibitors	9 major orthopaedic	Continuous rFVIIa	8/9 (88.9%) bleeding controlled at end of surgery
Mancuso ME et al. 2016[25]	Single-centre, prospective, observational study	10 HA patients with inhibitors	11 major orthopaedic	Bolus doses of: • rFVIIa • aPCC • Sequential therapy with rFVIIa and aPCC	10/11 (91%) bleeding controlled
Mauser-Bunschoten EP et al. 1998[16]	Multicentre, retrospective observational study	3 HA patients with inhibitors	2 dental extraction 2 hip arthroplasty	Continuous rFVIIa	3/4 (75%) bleeding controlled
Mauser-Bunschoten EP et al. 2002[17]	Multicentre, prospective observational study	4 HA patients and 1 HB patient with inhibitors	2 synovectomy 4 dental extraction 1 orthopaedic surgery	Continuous rFVIIa	NR (except 2 dental extractions rated 'ineffective' and 2 rated 'partially effective')
Négrier C et al. 2013[93]	Multicentre, prospective, observational study	18 HA patients and 2 HB patients with inhibitors	35 various (including procedures performed on n=4 acquired haemophilia patients)	Bolus aPCC	31/34 (91%) bleeding controlled (rated as 'excellent' or 'good'; full population including acquired haemophilia patients; concomitant medication documented in n=34/35 surgical procedures)
Pruthi RK et al. 2007[19]	Multicentre, prospective interventional study	24 HA/HB patients with inhibitors (A/B subgroups not specified)	24 elective surgery	Bolus and continuous infusion of rFVIIa	17/23 (74%) bleeding controlled overall (n=1 patient excluded from efficacy analysis)

Study	Study design	Patients	Procedures	Haemostatic treatment	Haemostatic outcome
Quintana-Molina M et al. 2004[65]	Single-centre, retrospective observational study	45 HA patients 3 HB patients with inhibitors	10 major elective and emergency 54 minor elective and emergency	Bolus doses of: • rFVIIa, or • aPCC, or • FVIII concentrate	• rFVIIa: 14/18 (78%) bleeding controlled • aPCC: 31/32 (97%) bleeding controlled • FVIII concentrate: 15/15 (100%) bleeding controlled (based on outcomes reported in article tables)
Santagostino E et al. 2001[97]	Multicentre, prospective, observational study	25 HA patients with inhibitors (unclear how many had surgery)	11 major 14 minor	Continuous rFVIIa	Surgical patients' results not reported separately
Scharrer I. 1999[15]	Multicentre, prospective interventional study	19 HA/HB patients with inhibitors (A/B subgroups not specified)	5 major 17 minor (full population including patients with acquired inhibitors/FVII deficiency)	Bolus rFVIIa	100% minor/60% major surgical procedures bleeding controlled (during surgery)
Serban M et al. 2014[21]	Single-centre, retrospective observational study	13 HA/B patients with inhibitors (not clear whether A or B)	Invasive orthopaedic (n NR)	Bolus doses and continuous infusion of: • FVIII/FIX concentrates • rFVIIa	Reported but not for population of interest
Shapiro AD et al. 1998[73]	Multicentre, prospective interventional study	25 HA patients and 3 HB patients with inhibitors	29 (including 1 procedure for a patient with acquired haemophilia): 11 major 18 minor	Bolus rFVIIa	23/29 (79%) bleeding controlled (may include 1 acquired haemophilia patient's procedure)
Smith MP et al. 2001[18]	Multicentre, prospective interventional study	6 HA patients with inhibitors	6 major	Bolus dose followed by continuous infusion of rFVIIa	2/6 bleeding controlled
Smith OP et al. 2002[75]	Two-centre, retrospective chart review	12 HA patients with inhibitors	19 CVAD insertion/removal 1 multiple dental extraction	Bolus rFVIIa	20/20 (100%) bleeding controlled (n=2 cases of minor bleeding after treatment had ended were resolved with re-treatment of rFVIIa)
Tjonnfjord GE. 2004, 2006[100, 101]	Single-centre, retrospective observational study	8 HA patients with inhibitors	12 minor 6 major	Bolus aPCC	18/18 (100%) bleeding controlled

aPCC: Activated prothrombin complex concentrate; CVAD: Central venous access device; FIX: Factor IX; FVII: Factor VII; FVIII: Factor VIII; HA: Haemophilia A; HB: Haemophilia B; NR: Not reported; pdFVIII: Plasma-derived factor VIII; rFVIIa: Recombinant factor VIIa; rFVIII: Recombinant factor VIII; TXA: Tranexamic acid

Table 3

Table 3: Routine Laboratory Testing

Study	Monitoring methods	Monitoring results
Balkan C et al. 2010[12]	Laboratory assessment (post-operative) of: • Platelet count • PT • APTT • Fibrinogen • D-dimer	• APTT did not return to normal by using the haemostatic agents • Significant shortening of PT
Gatti L et al. 1984[13]	Laboratory assessment of: • Clinical effectiveness • The prevalence of anamnestic antibody responses and of severe or milder side effects • Platelet counts • Haematocrit	NR
Habermann B et al. 2004[23]	Laboratory assessment of: • D-dimer	• Only on the day of surgery was a slight increase of the D-dimer level seen. On the postoperative days, the D-dimer levels were within the normal range.
Ingerslev J. et al. 1996[49]	Laboratory assessment of: • Platelet count • PT • APTT • Fibrinogen • D-dimer • ATIII	• Small reductions in platelet numbers • Significantly shortened PT following infusion • APTT shortened in nearly all patients • Insignificant changes in fibrinogen • All but one D-dimer sample showed results below the limits of specified abnormality • ATIII showed no tendency to decrease
Kraut EH et al. 2007[14]	Laboratory assessment, including platelet function analysis, of: • D-dimer levels • Haemoglobin level • Aggregation	• aPCC treatment was reduced after monitoring indicated an elevation in D-dimer levels
Lauroua P et al. 2009[54]	Consumption coagulopathy and thrombogenicity evaluated with laboratory assessment of: • Platelets • Fibrinogen • D-dimer or fibrinogen and fibrin degradation products • Haemoglobin level	• Monitoring of D-dimer, fibrinogen and fibrin degradation products showed no consistent activation of coagulation or increase in fibrinolysis • Neither platelet consumption nor fibrinogen depletion observed post-operatively • Haemoglobin remained stable above 8 g/dL in most cases
Ludlam A et al. 2003[10]	Laboratory assessment of: • Complete blood counts • Fibrinogen • D-dimer • ATIII (assessed by chromogenic determination)	• ATIII, fibrinogen and platelet counts fluctuated but did not decline progressively • During the first 72 h of infusion, mean platelet count decreased; Mean ATIII decreased between wound closure and at 72 h

Study	Monitoring methods	Monitoring results
Mancuso ME et al. 2016[25]	Laboratory assessment of: • Fibrinogen (Functional Clauss method) • D-dimer (Latex enhanced turbidimetric immunoassay) • PT (PT-based one-stage assay)	• D-dimer significantly increased over the first four post-operative days • Fibrinogen slightly decreased on the first post-operative day, then increased for the following three post-operative days • PT increased slightly in aPCC-treated patients over four post-operative days
Mauser-Bunschoten EP et al. 1998[16]	Laboratory assessment of: • PT	NR
Mauser-Bunschoten EP et al. 2002[17]	Laboratory assessment of: • PT	NR
Négrier C et al. 2013[93]	Laboratory assessment of: • Haemoglobin • Red blood cell count • Haematocrit • Liver enzyme levels	• Abnormal, significant haemoglobin levels were observed in 5 patients with inhibitors
Pruthi RK et al. 2007[19]	Laboratory assessment of: • Fibrinogen • D-dimer • PT	• No statistically significant differences between pre- and postoperative platelet counts, fibrinogen, D-dimer and F 1.2 concentrations between bolus infusion, continuous infusion or control subjects
Quintana-Molina M et al. 2004[65]	Laboratory assessment (postoperative and control tests at least every 48 hours) of: • Platelet count (obtained by impedance and optically) • PT and cephaline time (monitored by two apparatuses based on different techniques, either optical density or magnetic force) • Fibrinogen (Clauss method) • D-dimer (turbidimetry)	NR
Santagostino E et al. 2001[97]	Laboratory assessment of: • PT • APTT • Fibrinogen • D-dimer • Platelet count	• Platelet count decreased during 2 courses of treatment given for knee replacement
Scharrer I. 1999[15]	Laboratory assessment of PT and APTT plus: • Fibrinogen, or • Platelets, or	NR (Laboratory results only collected if considered necessary by the investigator and adverse event had occurred)

Study	Monitoring methods	Monitoring results
	• Thrombin-antithrombin complex, or • D-dimer, or • Fibrino-peptide A, or • Fibrin-degradation products, or • Fibrin monomer, or • ATIII, or • α-antiplasmin	
Shapiro AD et al. 1998[73]	Laboratory assessment of: • PT • Fibrinogen • D-dimer • ATIII • Platelet count	• Mean PT decreased • D-dimer levels increased in 83% of patients during the first 48 h postoperatively • No changes in ATIII • Mean fibrinogen levels increased • No change in platelet levels
Smith MP et al. 2001[18]	Laboratory assessment of: • International normalised ratio • Fibrinogen (Clauss method) • ATIII • Automated full blood counts • D-dimer	• ATIII, fibrinogen and platelet counts were not observed to decline
Smith OP et al. 2002[75]	Laboratory assessment of: • PT levels	• PT shortened to lower limit of normal following rFVIIa treatment • Some haemoglobin levels dropped below 8 g/dL in patients who experienced bleeding epsiodes
Tjonnfjord GE. 2004, 2006[100, 101]	Laboratory assessment of: • PT • APTT • Fibrinogen • D-dimer	PT shortened

aPCC: Activated prothrombin complex concentrate; APTT: Activated partial thromboplastin time; ATIII: Antithrombin; NR: Not reported; PT: Prothrombin time

Table 4: Factor VII Monitoring

Study	Haemostatic treatment	Reported factors monitored	Method of monitoring	Monitoring results
Ingerslev J. et al. 1996[49]	Bolus rFVIIa	Levels of post-infusion FVII:C	Laboratory assessment	NR
Ludlam A et al. 2003[10]	Continuous rFVIIa	• FVII:C • FVIIa:C levels	• Plasma FVII:C was assessed by an automated one-stage FVII clot method on an automated laboratory analyser • FVIIa:C was assessed using a specific automated assay	• Mean (range) FVII:C levels: ○ Effective haemostasis, end of surgery: 37 IU/ml, (29–51 IU/ml), n=8 ○ Ineffective haemostasis, end of surgery: 27 IU/ml, n=1 ○ Effective haemostasis, 8h after wound closure: 38 IU/ml (24–79 IU/ml), n=5 ○ Partially effective haemostasis, 8h after wound closure: 42 IU/ml, (37–57 IU/ml), n=4 • Mean (range) FVIIa:C levels: ○ Effective haemostasis, end of surgery: 50 IU/ml, (37–59 IU/ml), n=8 ○ Ineffective haemostasis, end of surgery: 40 IU/ml, n=1 ○ Effective haemostasis, 8h after wound closure: 52 IU/ml (37–74 IU/ml), n=5 ○ Partially effective haemostasis, 8h after wound closure: 61 IU/ml, (38–82 IU/ml), n=4 • FVII:C was >30 IU/ml at time of all but one bleeds
Mauser-Bunschoten EP et al. 1998[16]	Continuous rFVIIa	Plasma FVIIa levels	FVIIa: one-stage coagulation assay	• FVIIa levels maintained above 10 U/ml through flow rate adjustment
Mauser-Bunschoten EP et al. 2002[17]	Continuous rFVIIa	Plasma FVIIa levels	FVIIa: one-stage coagulation assay	NR
Pruthi RK et al. 2007[19]	Bolus and continuous infusion of rFVIIa	FVII:C	Samples for FVII:C were collected within 30 min prior to and at 10 min after the initial 90 µg/kg rFVIIa bolus infusion, at 0, 8, 24, 48 and 72 h after wound closure and daily from post-operative day 4 –10 or until discharge (and prior to any supplemental bolus	• At wound closure, FVII:C levels were higher in continuous vs. bolus infusion patients, which as sustained through 72 h but not statistically significant • In subjects for whom therapy was ineffective, FVII:C levels were in excess of 30 IU/ml at the time therapy was declared ineffective

Study	Haemostatic treatment	Reported factors monitored	Method of monitoring	Monitoring results
			infusion of rFVIIa). FVII:C was measured in a central laboratory	
Santagostino E et al. 2001[97]	Continuous rFVIIa	FVII:C	One-stage coagulation assay	• FVII:C levels were significantly higher during continuous infusion courses given for major surgery than minor surgery • rFVIIa clearance was significantly lower in courses given for major surgery than for minor surgery
Shapiro AD et al. 1998[73]	Bolus rFVIIa	FVII:C	Laboratory analysis of blood sample	• FVII:C could not be analysed in terms of haemostatic outcome due to timings of blood sampling
Smith MP et al. 2001[18]	Bolus dose followed by continuous infusion of rFVIIa	FVII:C	Laboratory assessment	• Target FVII:C of 10 IU/dl was found to be insufficient to prevent bleeding

FVII:C: Factor VII coagulation activity; FVIIa:C: Factor VIIa coagulation activity; FVIIa: Factor VIIa; NR: Not reported; rFVIIa: Recombinant factor VIIa

Table 5: TEG/ROTEM Analysis

Study	Haemostatic treatment	Reported factors monitored	Method of monitoring	Monitoring results
Furukawa S et al. 2015[20]	• rFVIIa, or • aPCC	Coagulation process: • Clotting time • Clot formation time	ROTEM	• Clotting time and clot formation time ROTEM parameters shortened significantly after infusion of bypassing products • Clot formation time was shorter than normal in most cases after treatment with rFVIIa
Holmström M et al. 2012[22]	Bolus aPCC in combination with TXA	Whole blood coagulation profiles	ROTEM	• During surgery, TEG showed significant improvement in CT, MaxVel and tMaxVel after aPCC and TXA and MCF increased towards normal • No significant difference in CT or MaxVel between different TXA concentrations • Significant increase in clot stability, shown by MCF, in a dose-dependent manner
Serban M et al. 2014[21]	Bolus doses and continuous infusion of: • FVIII/FIX concentrates • rFVIIA	FVIII/FIX activity	TEG	NR

aPCC: Activated prothrombin complex concentrate; CT: Clotting time; FIX: Factor IX; FVIII: Factor VIII; MaxVel: Maximum velocity of clot formation; MCF: Maximum clot formation; NR: Not reported; rFVIIa: Recombinant factor VIIa; ROTEM: Rotational thromboelastometry; TEG: Thromboelastography; tMaxVel: Time until maximum velocity; TXA: Tranexamic acid

Table 6

Table 6: Factor VIII:C

Study	Haemostatic treatment	Reported factors monitored	Method of monitoring	Monitoring results
Porcine FVIII:C				
Gatti L et al. 1984[13]	• Bolus porcine FVIII (Hyate:C) (minor dental), or • Continuous porcine FVIII (Hyate:C) (major)	• The antibody cross-reactivity with porcine FVIII • The relationship between preinfusion antibody titre, FVIII dosage given and its postinfusion plasma levels • The problems of 'resistance'	• Platelet counts and haemotocrits were measured with standard methods • FVIII coagulant activity measured by a one-stage method • Anti-human FVIII antibody measured in fresh plasma by the Bethesda assay method • Anti-porcine FVIII antibody measured using method based on same principles as Bethesda assay	• Haemostatic efficacy was dependent on achieving and maintaining target levels of FVIII:C (40-50 U/dl for dental surgery) • FVIII:C was used to identify cases of 'resistance' to bypassing therapy, with treatment adjusted as appropriate
Human FVIII:C				
Danielson H et al. 2017[24]	• Cryoprecipitate, or • Coagulation FVIII (pdFVIII or rFVIII), or • aPCC, or • rFVIIa (post-treatment switch in some individual cases)	• FVIII:C • Development of disseminated intravascular coagulation, anaemia, or thrombocytopenia	Routine blood coagulation test	• One patient experienced a decline in FVIII:C which led to a treatment switch
Habermann B et al. 2004[23]	Anvitoff™ (containing TXA) plus bolus FVIII or continuous rFVIIa infusion	FVIII:C levels and inhibitors	Laboratory assessment	• A decrease of FVIII levels down to zero was measured on days 4–6 in all patients substituted with FVIII. Simultaneously an increase of the inhibitors against FVIII was noticed
Holmström M et al. 2012[22]	Bolus aPCC in combination with TXA	FVIII:C	One-stage clotting assay (FVIII activity)	NR
Serban M et al. 2014[21]	Bolus doses and continuous infusion of: • FVIII/FIX concentrates • rFVIIa	FVIII/FIX activity	Laboratory assessment	NR

aPCC: Activated prothrombin complex concentrate; FIX: Factor IX; FVIII: Factor VIII; FVIII:C: Factor VIII coagulation activity; NR: Not reported; pdFVIII: Plasma-derived factor VIII; rFVIIa: Recombinant factor VIIa; rFVIII: Recombinant factor VIII; TXA: Tranexamic acid

Table 7: Thrombin Generation

Study	Haemostatic treatment	Factors monitored	Method of monitoring	Monitoring results
Holmström M et al. 2012[22]	Bolus aPCC in combination with TXA	LT, ETP, peak and ttPeak	TGA (on platelet-poor plasma)	• TGA showed shortened LT, ttPeak and a higher ETP and peak after aPCC + TXA administration compared to baseline, but not exceeding the values of healthy controls
Mancuso ME et al. 2016[25]	Bolus doses of: • rFVIIa • aPCC • Sequential therapy with rFVIIa and aPCC	Platelet count	TGA	• No significant difference was found in TGA values (PRP and PPP) measured during the postoperative period by comparing procedures with (n=7) and without (n=4) bleeding complications (data not shown)

aPCC: Activated prothrombin complex concentrate; ETP: Endogenous thrombin potential; LT: Lagtime; PRP: Platelet-rich plasma; PPP: Platelet-poor plasma; rFVIIa: Recombinant factor VIIa; TGA: Thrombin generation assay; ttPeak: Time to peak; TXA: Tranexamic acid

SUPPLEMENTARY DATA

Supplementary Table 1. Search Terms for MEDLINE and Embase (Searched via the Ovid SP Platform)

Term group	#	Searches	Hits
Patients with haemophilia	1	exp *HEMOPHILIA A/ or exp *HEMOPHILIA B/	32,171
	2	(hemophilia* or haemophilia*).tw.	49,984
	3	1 or 2	54,867
Intervention	4	(surger* or surgic* or operat* or procedure* or dental).tw.	6,877,475
	5	exp *surgical procedures, operative/	3,914,616
	6	4 or 5	8,936,274
Patients with inhibitors	7	(inhibitor* or alloantibod* or immune toler* or autoantibod*).tw.	2,648,102
Exclusion terms	8	(conference abstract or conference review).pt.	2,946,970
	9	limit 8 to yr="1946-2014"	1,907,607
	10	exp Animals/ not exp humans/	9,104,800
Combined	11	9 or 10	10,832,433
	12	3 and 6 and 7	2,925
	13	12 not 11	2,200
Total	14	remove duplicates from 13	1,383

MEDLINE, MEDLINE In-Process, MEDLINE Daily and MEDLINE Epub Ahead of Print (1946 to present); Embase (1974 to 23 March 2018).

Supplementary Table 2. Search Terms for The Cochrane Library (Searched via the Wiley Online Platform)

Term group	#	Searches	Hits
Patients with haemophilia	1	[mh "hemophilia A"] or [mh "hemophilia B"]	340
	2	(hemophilia* or haemophilia*):ti,ab,kw	1,019
	3	#1 or #2	1,019
Intervention	4	(surgery* or surgic* or operat* or procedure* or dental):ti,ab,kw	286,413
	5	[mh "surgical procedures, operative"]	122,148
	6	#4 or #5	334,058
Patients with inhibitors	7	(inhibitor* or alloantibod* or immune toler* or autoantibod*):ti,ab,kw	76,222
Total	8	#3 and #6 and #7 in Cochrane Reviews (Reviews and Protocols), Other Reviews and Trials	98

The Cochrane Database of Systematic Reviews (CDSR): Issue 3 of 12, March 2018; The Database of Abstracts of Reviews of Effects (DARE): Issue 2 of 4, April 2015; The Cochrane Central Register of Controlled Trials (CENTRAL): Issue 2 of 12, February 2018.

Supplementary Table 3. Search Terms for Congress Proceedings

Congress	Link	Search strategy	Hits
American Society of Hematology (ASH) Annual Meeting (2015, 2016, 2017)	2015: http://www.bloodjournal.org/content/126/23 2016: http://www.bloodjournal.org/content/128/22 2017: http://www.bloodjournal.org/content/130/Suppl_1	The following terms were searched one by one for both years: • Hemophil • Haemophil	2015: 34 2016: 26 2017: 10
British Society for Haematology (BSH) Annual Scientific Meeting (2016, 2017)	2016: Abstract book was in PDF form 2017: Abstract book was in PDF form	The following terms were searched one by one for both years: • Hemophil • Haemophil	2016: 6 2017: 7
European Association for Haemophilia and Allied Disorders (EAHAD) Annual Congress (2016, 2017)	2016: Abstract book was in PDF form 2017: Abstract book was in PDF form	The following terms were searched one by one for both years: • Surg • Operat • Proced • Dental	2016: 54 2017: 53
Haemophilia and thrombosis research society (HTRS) Scientific Symposium (2015, 2017)	2015: Abstract book was in PDF form 2017: Abstract book was in PDF form	The following terms were searched one by one for both years: • Surg • Operat • Proced • Dental	2015: 14 2017: 20
European Haemophilia Consortium (EHC) Annual Conference (2015, 2016)	*Abstract books for 2015 and 2016 were unavailable so were not searched*		
European Hematology Association (EHA) Congress (2016, 2017)	2016: Abstract book was in PDF form 2017: Abstract book was in PDF form	The following terms were searched one by one for both years: • Hemophil • Haemophil	2016: 27 2017: 13
International Society for Thrombosis and Haemostasis (ISTH) Congress (2016, 2017)	2016: Abstract book was in PDF form 2017: Abstract book was in PDF form and the website was also searched (http://www.professionalabstracts.com/isth2017/iplanner/#/grid)	The following terms were searched one by one for both years: • Surg • Operat • Proced • Dental	2016: 59 2017: 100
World Federation of Hemophilia (WFH) World Congress (2016)	Abstract book was in PDF form	The following terms were searched one by one: • Surg • Operat • Proced • Dental	79

Supplementary Table 4. Eligibility Criteria for the Systematic Review

PICOS domain	Inclusion criteria	Exclusion criteria
Population	Haemophilia A patients with inhibitors at time of surgery Haemophilia B patients with inhibitors at time of surgery Patients with acquired haemophilia	Haemophilia A patients without inhibitors (at time of surgery) Haemophilia B patients without inhibitors (at time of surgery)
Intervention(s)	Patients undergoing surgery (haemophilia-related or unrelated procedures, including dental procedures)	Patients not undergoing surgical procedures
Comparator(s)	Any or none	No exclusion criteria
Outcomes	Details of perioperative management employed in the population of interest, including: • Monitoring of haemoglobin • Monitoring of haemostatic efficacy • Need to change dosing of haemostatic treatment or need for change in treatment • Use of thromboprophylaxis • Use of antifibrolytics • Laboratory monitoring of global haemostasis (ROTEM, TEG, thrombin generation assessment) • Duration of treatment Outcomes relating to the success of perioperative management, including: • Bleeding control • Wound healing outcomes • Survival • Re-operation/re-admission • Infection rates • Other management-related complications	Studies not reporting outcomes related to monitoring or management of haemophilia patients for surgery
Study design	All study designs Any study presenting original data was eligible for inclusion	Studies not presenting original data were excluded
Other considerations	Studies with abstracts or full-texts in the English language Only studies with human participants were included	Studies not published in the English language Animal studies were excluded

ROTEM: Rotational thromboelastometry; TEG: Thromboelastography

Supplementary Table 5. Studies Excluded After Full Text Screening

Study	Reason for Exclusion
Al-Salama ZT, Scott LJ. Lonoctocog Alfa: A Review in Haemophilia A. Drugs 2017;77:1677-1686.	Study design
Arkin S, Cooper HA, Hutter JJ, et al. Activated recombinant human coagulation factor VII therapy for intracranial hemorrhage in patients with hemophilia A or B with inhibitors: Results of the novoseven emergency-use program. Haemostasis 1998;28:93-98.	Wrong population
Balta A, Tornemo M, Radulovic V, et al. Monitoring of treatment with bypassing agents in patients with acquired and congenital haemophilia with inhibitors using ROTEM: A single-centre experience. Haematologica 2015;100:669-670.	Wrong population
Bayram I, Erbey F, Erdem S, et al. Recombinant factor VIIa and activated prothrombin-complex concentrate administration in the management of bleeding, coagulopathy and intractable coagulopathy in pediatric patients undergoing invasive medical procedures or surgery. UHOD - Uluslararasi Hematoloji-Onkoloji Dergisi 2009;19:205-212.	Wrong population
Bedoya M, Acord M, Srinivasan A, et al. Implantable venous access devices in boys with severe hemophilia: At a tertiary pediatric institution. Pediatric Radiology 2017;47:S86.	Irrelevant intervention
Berger K, Frey L, Spannagl M, et al. Health economic aspects of the use of blood and blood products. [German]. Bundesgesundheitsblatt, Gesundheitsforschung, Gesundheitsschutz 2006;49:64-72.	Study design
Berntorp E, Astermark J, Baghaei F, et al. Treatment of haemophilia A and B and von Willebrand's disease: summary and conclusions of a systematic review as part of a Swedish health-technology assessment. Haemophilia 2012;18:158-65.	Study design
Biron-Andreani C, de Moerloose P, D'Oiron R, et al. Cancer detection and management in patients with haemophilia: A retrospective European multicentre study. Haemophilia 2013;20:78-82.	Irrelevant intervention
Birschmann I, Klamroth R, Eichler H, et al. Results of the WIRK prospective, non-interventional observational study of recombinant activated factor VII (rFVIIa) in patients with congenital haemophilia with inhibitors and other bleeding disorders. Haemophilia 2013;19:679-685.	Irrelevant intervention
Blanchette VS, al-Musa A, Stain AM, et al. Central venous access catheters in children with haemophilia. Blood Coagulation & Fibrinolysis 1996;7 Suppl 1:S39-44.	Irrelevant intervention
Boardman KP, English P. Fractures and dislocations in hemophilia. Clinical Orthopaedics and Related Research 1980;No. 148:221-232.	Irrelevant intervention
Bona RD, Weinstein RA, Weisman SJ, et al. The use of continuous infusion of factor concentrates in the treatment of hemophilia. American Journal of Hematology 1989;32:8-13.	Irrelevant intervention
Borhany M, Abid M, Fatima N, et al. Hemophilia care in Pakistan. Blood Transfusion 2017;15 (Supplement 3):s493.	Irrelevant intervention
Bulik O, Bulikova A, Smejkal P, et al. Preparation of patients with haemostasis disorder for dental surgery. [Czech]. Vnitrni Lekarstvi 2008;54:415-420.	Study design
Caviglia H, Candela M, Landro ME, et al. Haemophilia pseudotumours in patients with inhibitors. Haemophilia 2015;21:681-685.	Study design
Colvin BT. Role of plasma-exchange in the management of patients with factor VIII inhibitors. La Ricerca in clinica e in laboratorio 1983;13:85-93.	Study design
Cooper HA, Gilchrist GS, Hoots WK, et al. Comparison of two doses of recombinant factor Vlla (rFVlla) for producing hemostasis during and after surgery in patients (PTS) with hemophilia A or B and inhibitors and PTS with acquired inhibitors. Blood 1997;90:600a.	Study design

Study	Reason for Exclusion
Coppola A, Minno M, Tufano A, et al. Treatment for preventing bleeding in people with congenital bleeding disorders undergoing surgery: A systematic review of randomised controlled trials. Thrombosis research. Volume 134, 2014:S4-s5.	Study design
Coppola A, Windyga J, Tufano A, et al. Treatment for preventing bleeding in people with haemophilia or other congenital bleeding disorders undergoing surgery. The Cochrane database of systematic reviews 2015;2:CD009961.	Study design
Dargaud Y, Lienhart A, Negrier C. Prospective assessment of thrombin generation test for dose monitoring of bypassing therapy in hemophilia patients with inhibitors undergoing elective surgery. Blood 2010;116:5734-5737.	Study design
Dargaud Y, Pavlova A, Lacroix-Desmazes S, et al. Achievements, challenges and unmet needs for haemophilia patients with inhibitors. Haemophilia 2016;22:1-24.	Study design
Dekoven M, Wisniewski T, Petrilla A, et al. Patient/caregiver perceived benefits and barriers to elective orthopedic surgery (EOS) in patients with congenital hemophilia with inhibitors. Journal of Medical Economics 2012;15:305-312.	Irrelevant intervention
Domm JA, Hudson MG, Janco RL. Complications of central venous access devices in paediatric haemophilia patients. Haemophilia 2003;9:50-56.	Irrelevant intervention
Economou M, Teli A, Adremerina A, et al. Absence of thrombotic complications with the use of bypassing agents in young hemophilia patients with inhibitor presence. Haemophilia 2018;24 (Supplement 1):105.	Irrelevant intervention
Escobar M, Maahs J, Hellman E, et al. Multidisciplinary management of patients with haemophilia with inhibitors undergoing surgery in the United States: Perspectives and best practices derived from experienced treatment centres. Haemophilia 2012;18:971-981.	Study design
Furukawa S, Nogami K, Ogiwara K, et al. Systematic monitoring of hemostatic management in hemophilia A patients with inhibitor in the perioperative period using rotational thromboelastometry. Journal of Thrombosis and Haemostasis 2015;13:350.	Duplicate
Galstian GM, Spirin M, Zozulya N, et al. Providing hemostasis for long-term central venous access device (LTCVAD) placement in patients with factor VIII (fVIII) inhibitors. Blood. Conference: 59th Annual Meeting of the American Society of Hematology, ASH 2017;130.	Irrelevant intervention
Ghosh K, Shetty S, Jijina F, et al. Role of epsilon amino caproic acid in the management of haemophilic patients with inhibitors. Haemophilia 2004;10:58-62.	Wrong population
Givol N, Hirschhorn A, Lubetsky A, et al. Oral surgery-associated postoperative bleeding in haemophilia patients - a tertiary centre's two decade experience. Haemophilia 2015;21:234-240.	Irrelevant intervention
Goodnight Jr SH, Common HH, Lovrien EW. Factor VIII inhibitor following surgery for epidural hemorrhage in hemophilia: successful therapy with a concentrate containing factors II, VII, IX, and X. Journal of Pediatrics 1976;88:357-358.	Wrong population
Gozden HE, Ozkalemkas F, Ozkocaman V, et al. Evaluation of patients with hemophilia; Uludag University experience. Thrombosis Research 2016;141:S37.	Wrong population
Haque Q, Feng X, Abuduaini Y. Intracranial haemorrhage in children with inherited bleeding disorders: A single center study in China. Hong Kong Journal of Paediatrics 2018;23(1):69.	Irrelevant intervention
Haque Q, Li C, Abuduaini Y, et al. Intracranial hemorrhage in children with inherited bleeding disorders: A single center study in China. Blood. Conference: 59th Annual Meeting of the American Society of Hematology, ASH 2017;130.	Duplicate
Hay CRM, Negrier C, Ludlam CA. The treatment of bleeding in acquired haemophilia with recombinant factor VIIa: A multicentre study. Thrombosis and Haemostasis 1997;78:1463-1467.	Irrelevant intervention
Hedner U. Factor VIIa in the treatment of haemophilia. Blood coagulation & fibrinolysis: an international journal in haemostasis and thrombosis 1990;1:307-317.	Study design

Study	Reason for Exclusion
Hirose J, Takedani H, Koibuchi T. The risk of elective orthopaedic surgery for haemophilia patients: Japanese single-centre experience. Haemophilia 2013;19:951-955.	Irrelevant intervention
Holmstrom M, Astermark J, Brodin E, et al. Swedish national registry for bleeding disorders-first report. Haemophilia 2018;24 (Supplement 1):101.	Wrong population
Hvid I, Rodriguez-Merchan EC. Orthopaedic surgery in haemophilic patients with inhibitors: An overview. Haemophilia 2002;8:288-291.	Study design
Jones ML, Wight J, Paisley S, et al. Control of bleeding in patients with haemophila A with inhibitors: A systematic review. Haemophilia 2003;9:464-520.	Study design
Kenet G, Lubetsky A, Gitel S, et al. Treatment of bleeding episodes in patients with hemophilia and an inhibitor: Comparison of two treatment protocols with recombinant activated factor VII. Blood Coagulation and Fibrinolysis 2000;11:S35-S38.	Wrong population
Kleinschmidt S, Plinkert PK, Fuchs-Buder T, et al. [Haemostatic disorders in ENT patients.Part 2: Pathophysiology, diagnostics, clinical feature and therapy]. HNO 2003;51:251-266.	Study design
Klintman J, Berntorp E. Epidemiological aspects of inhibitor development in hemophilia and strategies of management. Expert Opinion on Orphan Drugs 2016;4:153-168.	Study design
Klukowska A, Laguna P, Rawicz M. Procedures for CV catheters insertion in children with congenital coagulation disorders. [Polish]. Medycyna wieku rozwojowego 2008;12:1126-1129.	Irrelevant intervention
Kreuz W, Gill JC, Rothschild C, et al. Full-length sucrose-formulated recombinant factor VIII for treatment of previously untreated or minimally treated young children with severe haemophilia A: Results of an international clinical investigation. Thrombosis and Haemostasis 2005;93:457-467.	Wrong population
Kulkarni R, Presley RJ, Lusher JM, et al. Complications of haemophilia in babies (first two years of life): a report from the Centers for Disease Control and Prevention Universal Data Collection System. Haemophilia 2017;23:207-214.	Wrong population
Laguna P, Klukowska A. Management of oral bleedings with recombinant factor VIIa in children with haemophilia A and inhibitor. Haemophilia 2005;11:2-4.	Study design
Liesner RJ, Abashidze M, Aleinikova O, et al. Immunogenicity, efficacy and safety of Nuwiq (human-cl rhFVIII) in previously untreated patients with severe haemophilia A-Interim results from the NuProtect Study. Haemophilia 2017;16:16.	Irrelevant intervention
Lim MY, Nielsen B, Ma A, et al. Clinical features and management of haemophilic pseudotumours: A single US centre experience over a 30-year period. Haemophilia 2013;20:e58-e62.	Study design
Lulla RR, Allen GA, Zakarija A, et al. Transplacental transfer of postpartum inhibitors to factor VIII. Haemophilia 2010;16:14-17.	Wrong population
Lusher JM, Lee CA, Kessler CM, et al. The safety and efficacy of B-domain deleted recombinant factor VIII concentrate in patients with severe haemophilia A. Haemophilia 2003;9:38-49.	Irrelevant intervention
Makris M. Systematic review of the management of patients with haemophilia A and inhibitors. Blood Coagulation and Fibrinolysis 2004;15:S25-S27.	Study design
McPherson J, Teague L, Lloyd J, et al. Experience with recombinant factor VIIa in Australia and New Zealand. Haemostasis 1996;26:109-117.	Study design
Mingot-Castellano ME, Perez-Montes R, Canaro M, et al. Successful treatment of bleeding in acquired hemophilia A with activated prothrombin complex concentrate in Spain. Blood. Conference: 59th Annual Meeting of the American Society of Hematology, ASH 2017;130.	Irrelevant intervention

Study	Reason for Exclusion
Mortazavi SMJ, Najafi A, Toogeh G. Total joint replacement in haemophilia A patients with high titre of inhibitor using a new brand recombinant factor VIIa (Aryoseven). Haemophilia 2016;22:e451-e453.	Study design
Negrier C, Ragni MV, Georgiev P, et al. Perioperative management in patients with hemophilia receiving fitusiran, an investigational rnai therapeutic targeting antithrombin for the treatment of hemophilia. Blood. Conference: 59th Annual Meeting of the American Society of Hematology, ASH 2017;130.	Duplicate
Nilsson IM, Hedner U. Immunosuppressive treatment in haemophiliacs with inhibitors to factor VIII and factor IX. Scandinavian Journal of Haematology 1976;16:369-382.	Study design
Obergfell A, Auvinen MK, Mathew P. Recombinant activated factor VII for haemophilia patients with inhibitors undergoing orthopaedic surgery: A review of the literature. Haemophilia 2008;14:233-241.	Study design
Parameswaran R, Shapiro AD, Gill JC, et al. Dose effect and efficacy of rFVIIa in the treatment of haemophilia patients with inhibitors: Analysis from the Hemophilia and Thrombosis Research Society Registry. Haemophilia 2005;11:100-106.	Irrelevant intervention
Park YS. Preferences between surgical or medical treatment in hemophilia patients with spontaneous epidural hematoma may vary. Haemophilia 2018;24 (Supplement 1):133.	Irrelevant intervention
Pruthi RK, Mathew P, Valentino LA, et al. An open-label, randomized, parallel, multi-center trial comparing the safety and efficacy of rFVIIa when administered as IV bolus or IV continuous infusion to hemophilia patients with inhibitors during and after surgery. Blood 2004;104:3975.	Irrelevant intervention
Rodriguez-Merchan EC. Surgery in haemophilic patients with inhibitors. Haemophilia 2004;10 Suppl 2:1-2.	Duplicate
Rodriguez-Merchan EC, Wiedel JD, Wallny T, et al. Elective orthopaedic surgery for inhibitor patients. Haemophilia 2003;9:625-31.	Duplicate
Rudowski WJ. Major surgery in hemophilia. Annals of the Royal College of Surgeons of England 1981;63:111-117.	Irrelevant intervention
Salaj P, Louzil J, Geierova V, et al. Diagnosis and management of acquired haemophilia-single centre experience. Journal of Thrombosis and Haemostasis 2016;14:56.	Irrelevant intervention
Salcioglu Z, Sen HS, Tugcu D, et al. Congenital factor deficiencies: Twenty-five-year follow-up. Journal of Thrombosis and Haemostasis 2015;13:358-359.	Irrelevant intervention
Salzmann G, Schramm W, Feifel G. The hemophiliac as a surgical patient. [German]. Munchener Medizinische Wochenschrift 1977;119:677-684.	Wrong population
Schoppmann A, Jaeger K, Berg R, et al. Review of the literature of FEIBA administration in patients with hemophilia B and inhibitors. Journal of Coagulation Disorders 2011;3:14-26.	Study design
Schulz, S. Inhibitor hemophilia in oral surgery. [German]. Zahn-, Mund-, und Kieferheilkunde mit Zentralblatt 1984;72:824-848.	Non-English language
Schwartz RS, Abildgaard CF, Aledort LM, et al. Human recombinant DNA-derived antihemophilic factor (factor VIII) in the treatment of hemophilia A. New England Journal of Medicine 1990;323:1800-1805.	Wrong population
Seaman CD, Ragni MV. Sequential bypassing agents during major orthopedic surgery: a new approach to hemostasis. Blood Advances 2017;1:1309-1311.	Study design
See A, Sudirman SR, Huang XY. Spontaneous multilevel airway haemorrhage in acquired haemophilia A. European Archives of Oto-Rhino-Laryngology 2016:1-4.	Study design
Serban M, Mihailov D, Pop L, et al. Development of inhibitors in haemophilia. Hamostaseologie 2011;31:S20-S23.	Wrong population

Study	Reason for Exclusion
Serban M, Ursu E, Cernat L, et al. Thrombin generation and whole blood viscoelastic assays in the monitoring of haemophilia with inhibitors. Haematologica 2016;101:407.	Irrelevant intervention
Sholzberg M, Phua C, Tsui H, et al. Heparin and protamine confound factor activity and inhibitor testing while on cardiopulmonary bypass. Journal of Thrombosis and Haemostasis 2015;13:807.	Wrong population
Shutov SA, Kovalenko AV, Soboleva OA, et al. [Surgical treatment of the complication of urolithiasis in patients with inhibitor form of hemophilia]. Khirurgiia 2017:104-107.	Non-English language
Smith MP, Giangrande P, Pollman H, et al. A postmarketing surveillance study of the safety and efficacy of ReFacto (St Louis-derived active substance) in patients with haemophilia A. Haemophilia 2005;11:444-451.	Wrong population
Stachnik JM, Gabay MP. Continuous infusion of coagulation factor products. Annals of Pharmacotherapy 2002;36:882-891.	Study design
Stine KC, Shrum D, Becton DL. Use of FEIBA for invasive or surgical procedures in patients with severe hemophilia A or B with inhibitors. Journal of Pediatric Hematology/Oncology 2007;29:216-221.	Study design
Tjonnfjord GE, Brinch L, Gedde-Dahl III, et al. Activated prothrombin complex concentrate (FEIBA) treatment during surgery in patients with inhibitors to FVIII/IX. Haemophilia 2004;10:174-178.	Duplicate
Tuinenburg A, Damen SAJ, Ypma PF, et al. Cardiac catheterization and intervention in haemophilia patients: Prospective evaluation of the 2009 institutional guideline. Haemophilia 2013;19:370-377.	Study design
Valentino LA, Cooper DL, Goldstein B. Surgical Experience with rFVIIa (NovoSeven) in congenital haemophilia A and B patients with inhibitors to factors VIII or IX. Haemophilia 2011;17:579-589.	Study design
van Veen JJ, Maclean RM, Hampton KK, et al. Major surgery in severe haemophilia A with inhibitors using a recombinant factor VIIa and activated prothrombin complex concentrate hybrid regimen. Haemophilia 2014;20:587-592.	Study design
Varon D, Martinowitz U. Continuous infusion therapy in haemophilia. Haemophilia 1998;4:431-435.	Study design
Watts RG, Cook RP. Operative management and outcomes in children with congenital bleeding disorders: A retrospective review at a single haemophilia treatment centre. Haemophilia 2012;18:421-425.	Irrelevant intervention
Wensley RT, Stevens RF, Burn AM, et al. Plasma exchange and human factor VIII concentrate in managing haemophilia A with factor VIII inhibitors. British Medical Journal 1980;281:1388-1389.	Wrong population
White GC, 2nd. Seventeen years' experience with Autoplex/Autoplex T: evaluation of inpatients with severe haemophilia A and factor VIII inhibitors at a major haemophilia centre. Haemophilia 2000;6:508-12.	Irrelevant intervention
Windyga J, Stefanska-Windyga E, Odnoczko E, et al. Activated prothrombin complex concentrate in combination with tranexamic acid: a single centre experience for the treatment of mucosal bleeding and dental extraction in haemophilia patients with inhibitors. Haemophilia 2016;22:e465-e468.	Study design
Young G, Sidonio RF, Liesner R, et al. HAVEN 2 updated analysis: Multicenter, open-label, phase 3 study to evaluate efficacy, safety and pharmacokinetics of subcutaneous administration of emicizumab prophylaxis in pediatric patients with hemophilia a with inhibitors. Blood. Conference: 59th Annual Meeting of the American Society of Hematology, ASH 2017;130.	Irrelevant intervention

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Supplementary Table 6. Case Studies Excluded After Abstract Screening

Study
Abajas YL, Monahan PE, Neufeld EJ, et al. Novel approach for immunosuppression and peri-operative recombinant porcine factor viii replacement for pediatric congenital hemophilia a with high-titer inhibitor. American Journal of Hematology 2016;91 (9):E416.
Abildgaard CF, Penner JA, Watson-Williams EJ. Anti-inhibitor coagulant complex (Autoplex) for treatment of factor VIII inhibitors in hemophilia. Blood 1980;56:978-984.
Al-Trabolsi HA. Factor VIIa overdose: Clinical and laboratory observations. Current Pediatric Research 2004;8:19-21.
Ambaglio C, Preti PS, Sacco C, et al. Orthopaedic surgery in a patient affected by severe haemophilia a with inhibitors: Three surgeries-three different responses to bypassing agents. Haemophilia 2017;23:112-113.
Amici JM. Surgery of basal cell carcinoma in a man with hemophilia: Full thickness skin graft. [French]. Nouvelles Dermatologiques 2004;23:130-131.
Antic D, Elezovic I, Sufajdzic N, et al. Application of recombinant activated factor VII in treatment of intracranial haemorrhage in haemophilic patient with inhibitor. [Croatian]. Srpski arhiv za celokupno lekarstvo 2008;136 Suppl 3:218-221.
Aouba A, Dezamis E, Sermet A, et al. Uncomplicated neurosurgical resection of a malignant glioneuronal tumour under haemostatic cover of rFVIIa in a severe haemophilia patient with a high-titre inhibitor: A case report and literature review of rFVIIa use in major surgeries. Haemophilia 2010;16:54-60.
Apter B, McCarthy V, Shapiro SS, et al. Successful preoperative apheresis of factor VIII antibody using factor VIII concentrate as a replacement fluid. Journal of Clinical Apheresis 1986;3:140.
Ashrani AA, Reding MT, Shet A, et al. Successful liver transplantation in a patient with severe haemophilia A and a high-titre factor VIII inhibitor. Haemophilia 2004;10:735-737.
Banov L, Pavanello M, Piattelli G, et al. Successful urgent neurosugery management with rFVIIa mega doses in a child with haemophilia A and high titre inhibitor. Blood Coagulation and Fibrinolysis 2014;25:518-521.
Barbara DW, McKenzie KM, Parikh SA, et al. Successful perioperative management of severe bleeding from undiagnosed acquired factor VIII inhibitors. Journal of Cardiothoracic and Vascular Anesthesia 2015;29:731-734.
Batorova A, Morongova A, Tagariello G, et al. Challenges in the management of hemophilia B with inhibitor. Seminars in Thrombosis and Hemostasis 2013;39:767-771.
Bell BA, Birch K, Glazer S. Experience with recombinant factor VIIA in an infant hemophiliac with inhibitors to FVIII:C undergoing emergency central line placement: A case report. American Journal of Pediatric Hematology/Oncology 1993;15:77-79.
Bennetts NA, Mergelmeyer JE, Reimer EJ, et al. Initial Manifestation of Acquired Hemophilia A After a Routine Tooth Extraction. A Case Report and Literature Review. Journal of Oral and Maxillofacial Surgery 2018;76:490-494.
Berlocher WC, King DL. Considerations in the dental management of the factor VIII-deficient child with inhibitors. Pediatric dentistry 1979;1:188-191.
Bhave A, Srivastava A, Lee V, et al. Low-dose activated factor IX complex concentrates (FEIBA(R)) for post-operative haemostasis in a patient with high responding factor VIII inhibitors. Haemophilia 1995;1:274-6.
Biron-Andreani C, Dupeyron G, Mainemer M, et al. Successful use of recombinant factor VIIa in a haemophiliac with inhibitor undergoing cataract surgery. Blood Coagulation and Fibrinolysis 2001;12:215-216.
Blatt PM, Pearsall AH, Givhan EG, et al. Haemostatic failure of prothrombin complex concentrates during elective dental procedure. Thrombosis and Haemostasis 1980;42:1604-1606.

Study
Bona RD, Pasquale DN, Kalish RI, et al. Porcine factor VIII and plasmapheresis in the management of hemophiliac patients with inhibitors. American Journal of Hematology 1986;21:201-207.
Bontempo FA, Lewis JH, Spero JA, et al. Heart transplant in a hemophiliac with an acquired factor VIII inhibitor: Synthesis of factor VIII:C in pericardial fluid. Transplantation Proceedings 1988;20:790-791.
Boughton BJ, Payne A, Serman A, et al. Elective surgery in a haemophilic patient with high titre inhibitors: use of extracorporeal protein A immunoabsorption. Journal of Clinical Pathology 1990;43:172.
Brackmann HH, Effenberger W, Hess L, et al. Immune tolerance induction: A role for recombinant activated factor VII (rFVIIa)? European Journal of Haematology, Supplement 1998;61:18-23.
Briet E, van der Meer FW, van Dijk-van Kempen CJ, et al. Sequential administration of human and porcine factor VIII for surgical treatment of a parotid tumour in a patient with a factor VIII inhibitor. Acta Haematologica 1985;73:97-100.
Burk CD, Miller L, Handler SD, et al. Preoperative history and coagulation screening in children undergoing tonsillectomy. Pediatrics 1992;89:691-695.
Byhahn C, Lischke V, Westphal K. Translaryngeal tracheostomy in highly unstable patients. Anaesthesia 2000;55:678-682.
Candiotto L, Fullone FW, Ricciardi A, et al. Correction of knee flexion contracture at the time of surgical fixation of a femoral supracondylar fracture in a haemophiliac with inhibitors. Blood Transfusion 2015;13:333-335.
Carr Jr ME, Loughran TP, Cardea JA, et al. Successful use of recombinant factor VIIa for hemostasis during total knee replacement in a severe hemophiliac with high-titer factor VIII inhibitor. International journal of hematology 2002;75:95-99.
Castillo-Canadas AM, Serrano-Diana C, Lopez-Del Cerro E, et al. Diagnosis and treatment of hemophilia A acquired during postpartum. [Spanish]. Ginecologia y Obstetricia de Mexico 2014;82:688-696.
Caviglia H, Landro ME, Galatro GA, et al. Platelet rich in fibrin (PRF) in hemophilia. Haemophilia 2018;24 (Supplement 1):83.
Chau A, Wu J, Ansermino M, et al. A Jehovah's Witness child with hemophilia B and factor IX inhibitors undergoing scoliosis surgery. Canadian Journal of Anesthesia 2008;55:47-51.
Chen YC, Chang JY, Hsueh EJ, et al. Acquired hemophilia A: Report of two cases. Chinese Medical Journal (Taipei) 1998;61:538-544.
Chu M, Li H. Regional anesthesia in acquired hemophilia a (factor viii inhibitor positive). Regional Anesthesia and Pain Medicine. Conference: 41st Annual Regional Anesthesiology and Acute Pain Medicine Meeting of the American Society of Regional Anesthesia and Pain Medicine, ASRA 2016;41.
Chuansumrit A, Hathirat P, Keorochana S, et al. Disarticulation of a knee joint in a haemophiliac with high inhibitor titre. Haemophilia 1996;2:116-119.
Cooper HA, Jones CP, Campion E, et al. Rationale for the use of high dose rFVIIa in a high-titre inhibitor patient with haemophilia B during major orthopaedic procedures. Haemophilia 2001;7:517-522.
Croteau SE, Abajas YL, Wolberg AS, et al. Recombinant porcine factor VIII for high-risk surgery in paediatric congenital haemophilia A with high-titre inhibitor. Haemophilia 2017;23:e93-e98.
Damodar S, Bhat P, Kumar P, et al. Successful Aortic Valve Replacement Surgery in a Patient with Severe Haemophilia a with Low Titre Inhibitor. Indian Journal of Hematology and Blood Transfusion 2014;30:64-66.
Dargaud Y, Lienhart A, Meunier S, et al. Major surgery in a severe haemophlia A patient with high titre inhibitor: Use of the thrombin generation test in the therapeutic decision. Haemophilia 2005;11:552-558.
DeWitt RT, Feinstein DI. Prothrombin complex concentrate. Use in a hemophiliac with a factor VIII inhibitor. Archives of Internal Medicine 1977;137:1211-1213.

Study
Di Gaetano R, Belvini D, Salviato R, et al. Flow cytometry evaluation of INF-gamma and il-10 synthesis by T lymphocytes in a haemophilia a patient with inhibitor after infusion of FVIII. Blood Transfusion 2017;15 (Supplement 4):s545.
Divanon F, Hecquard C, Borel-Derlon A. Experience with use of recombinant activated factor VII. Journal of Clinical Pharmacy and Therapeutics 2002;27:133-138.
Dolatkhah R, Bazavar MR, Poureisa M, et al. Successful management of total knee replacement in a high responder hemophilia patient with a history of inhibitor. Iranian Red Crescent Medical Journal 2013;15:18-20.
Doughty HA, Coles J, Parmar K, et al. The successful removal of a bleeding intracranial tumour in a severe haemophiliac using an adjusted dose continuous infusion of monoclonal factor VIII. Blood Coagulation and Fibrinolysis 1995;6:31-34.
Doughty HA, Northheast A, Sklair L, et al. The use of recombinant factor VIIa in a patient with acquired haemophilia A undergoing surgery. Blood Coagulation and Fibrinolysis 1995;6:125-128.
Durham TM, Hodges ED, Harper J, et al. Management of traumatic oral-facial injury in the hemophiliac patient with inhibitor: case report. Pediatric dentistry 1993;15:282-287.
Eigner TL. Use of intraligamentary anesthesia in a patient with severe hemophilia and factor VIII inhibitor. Special care in dentistry : official publication of the American Association of Hospital Dentists, the Academy of Dentistry for the Handicapped, and the American Society for Geriatric Dentistry 1990;10:121-124.
Evans BE, Irving SP, Aledort LM. Use of microcrystalline collagen for hemostasis after oral surgery in a hemophiliac. Journal of Oral Surgery 1979;37:126-8.
Faradji A, Bonnomet F, Lecocq J, et al. Knee joint arthroplasty in a patient with haemophilia A and high inhibitor titre using recombinant factor VIIa (NovoSeven): A new case report and review of the literature. Haemophilia 2001;7:321-326.
Feistritzer C, Wildner SM, Wurtinger P, et al. Successful immune tolerance induction using turoctocog alfa in an adult haemophilia A patient. Blood Coagulation and Fibrinolysis 2017;28:181-184.
Forsyth A, Zourikian N. How we treat: Considerations for physiotherapy in the patient with haemophilia and inhibitors undergoing elective orthopaedic surgery. Haemophilia 2012;18:550-553.
Franchini M, Capra F, Capelli C, et al. Clinical efficacy of recombinant activated factor VII (rFVIIa) during acute bleeding episode and surgery in a patient with acquired hemophilia A with high inhibitor titer. Haematologica 2001;86:E12.
Frauchiger LH, Harstall R, Kajahn J, et al. Bilateral total knee arthroplasty in a patient with haemophilia A, high inhibitor titre and aneurysma spurium of the popliteal artery: A case report. Swiss Medical Weekly 2010;140.
Gay ND, Azar SS, Salomon O, et al. Management of a patient with factor XI deficiency with inhibitors undergoing cardiac surgery: A case report and review of the literature. American Journal of Hematology 2016;91 (9):E413.
Gillet B, Sigaud M, Ternisien C, et al. Can you predict the clinical efficacy of bypassing agents in patients with hemophilia and current inhibitor? Discussion about a case report in cardiovascular surgery. Haemophilia 2018;24 (Supplement 1):58.
Giuffrida G, Lombardo R, Parrinello NL, et al. Percutaneous transluminal angioplasty and stent implantation for aortic coarctation in haemophilia A patient with high-titre factor VIII inhibitors. Haemophilia 2014;20:e336-e338.
Goddard N. Case studies: Orthopaedic surgery in adult patients with haemophilia A with inhibitors. Haemophilia, Supplement 2005;11:32-37.
Gomes H, Martinez F, Robelo B, et al. Delayed diagnosis of pulmonary embolism in a patient with a prior history of acquired haemophilia. Haemophilia 2015;21:39.
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Goodknight SH, Common HH, Lovrein EW. Letter: Factor VIII inhibitor following surgery for epidural hemorrhage in hemophilia: successful therapy with a concentrate containing factors II, VII, IX, and X. The Journal of pediatrics 1976;88:356-357.
Gopalakrishnan N, Usha T, Thopalan B, et al. Hemodialysis in a patient with severe hemophilia A and factor VIII inhibitor. Hemodialysis International 2016;20:E11-E13.
Gorska-Kosicka M, Paluszkiewicz P, Krasowska D, et al. Uncontrolled postoperative bleeding in woman with pemphigus and undiagnosed acquired haemophilia A. [Polish]. Hematologia 2013;4:71-75.
Goudemand J, Tagariello G, Lopaciuk F. Cases of surgery in high-responder haemophilia patients. Haemophilia, Supplement 2004;10:46-49.
Gregg R, Lester W, Bramhall S, et al. Orthotopic liver transplantation in a patient with severe haemophilia A and a high-titre factor VIII inhibitor from an antithrombin-deficient cadaveric donor. Haemophilia 2013;19:e96-e97.
Griffen AL, Hoots WK, Carter AB. Activated prothrombin complex concentrates in the management of the hemophiliac with Factor VIII inhibitor: case report. Pediatric Dentistry 1987;9:321-4.
Gringeri A, Santagostino E, Mannucci PM. Failure of recombinant activated factor VII during surgery in a hemophiliac with high-titer factor VIII antibody. Haemostasis 1991;21:1-4.
Guglielmone H, Jarchum G, Minoldo S. Liver transplantation in a patient with mild haemophilia A and low-titres of factor VIII inhibitors treated with recombinant factor VIIa. The first Argentinean case. Haemophilia 2011;17:317-318.
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Heiland M, Weber M, Schmelzle R. Life-Threatening Bleeding After Dental Extraction in a Hemophilia A Patient With Inhibitors to Factor VIII: A Case Report. Journal of Oral and Maxillofacial Surgery 2003;61:1350-1353.
Heisel MA, Gomperts ED, McComb JG, et al. Use of activated prothrombin complex concentrate over multiple surgical episodes in a hemophilic child with an inhibitor. Journal of Pediatrics 1983;102:951-954.
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Ichikawa S, Kohata K, Okitsu Y, et al. Acquired hemophilia A with sigmoid colon cancer: Successful treatment with rituximab followed by sigmoidectomy. International Journal of Hematology 2009;90:33-36.
Ilg A, Stahlschmidt K, Zotz RB, et al. Interdisciplinary management of total knee replacement in a haemophilia patient with high-titre inhibitor and severe arthropathy complicated by an aneurysmatic bone cyst. Haemophilia 2009;15:377-9.
Ilkhchoui Y, Koshkin E, Windsor JJ, et al. Perioperative management of acquired hemophilia a: a case report and review of literature. Anesthesiology & Pain Medicine 2014;4:e11906.

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Isobe K, Koh K, Uehara T, et al. Successful sequential therapy using rfvii with a novel agent (plasma-derived factor fviia and factor fx mixture) to control perioperative bleeding in a patient with severe hemophilia a and inhibitors. Haematologica 2016;101:709.
Janic D, Brdar R, Kristic Z, et al. Successful concurrent triple surgery in an adolescent patient with haemophilia A and inhibitors treated with recombinant factor VIIa [2]. Haemophilia 2007;13:214-216.
Janic D, Brdar R, Krstic Z, et al. Successful concurrent triple surgery in an adolescent patient with haemophilia A and inhibitors treated with recombinant factor VIIa [4]. Haemophilia 2007;13:447-449.
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Jentzsch T, Brand-Staufer B, Schafer FP, et al. Illustrated operative management of spontaneous bleeding and compartment syndrome of the lower extremity in a patient with acquired hemophilia A: A case report. Journal of Medical Case Reports 2014;8 (1) (no pagination).
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Kanyike FB, Abdul-Salam SA, Prakash B, et al. Use of recombinant factor VIIa (NovoSeven) in a haemophilia A patient with inhibitor in Kuwait. Haemophilia 1999;5:273-275.
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Supplementary Table 7. Quality Assessment of Interventional Studies Reporting Perioperative Laboratory Monitoring

Study	Did the trial address a clearly focused issue?	Was the assignment of patients to treatments randomised?	Were all of the patients who entered the trial properly accounted for at its conclusion?	Were patients, health workers and study personnel 'blind' to treatment?	Were the groups similar at the start of the trial?	Aside from the experimental intervention, were the groups treated equally?	How large was the treatment effect?	How precise was the estimate of the treatment effect?	Can the results be applied in your context? (Or the local population?)	Were all clinically important outcomes considered?
Furukawa S et al. 2015[20]	Y	N	Y	N	N	N	–	–	Y	N
Gatti L et al. 1984[13]	Y	N	Y	N	–	–	–	–	N	Y
Ludlam A et al. 2003[10]	Y	N	Y	N	–	–	–	–	Y	Y
Mancuso ME et al. 2016[25]	Y	N	Y	N	N	N	–	–	Y	N
Pruthi RK et al. 2007[19]	Y	Y	Y	N	N	N	–	–	Y	Y
Santagostino E et al. 2001[97]	Y	N	Y	N	–	–	–	–	Unclear	Y
Scharrer I. 1999[15]	Y	N	Y	N	–	–	–	–	N	N
Shapiro AD et al. 1998[73]	Y	Y	Y	Y	Y	Y	–	–	Y	Y

Study	Did the trial address a clearly focused issue?	Was the assignment of patients to treatments randomised?	Were all of the patients who entered the trial properly accounted for at its conclusion?	Were patients, health workers and study personnel 'blind' to treatment?	Were the groups similar at the start of the trial?	Aside from the experimental intervention, were the groups treated equally?	How large was the treatment effect?	How precise was the estimate of the treatment effect?	Can the results be applied in your context? (Or the local population?)	Were all clinically important outcomes considered?
Smith MP et al. 2001[18]	Y	N	Y	N	–	–	–	–	Y	Y

Y: Yes; N: No

Supplementary Table 8. Quality Assessment of Observational Studies Reporting Perioperative Laboratory Monitoring

Study	Was the cohort recruited in an acceptable way?	Was the exposure accurately measured to minimise bias?	Was the outcome accurately measured to minimise bias?	Have the authors identified all important confounding factors?	Have the authors taken account of the confounding factors in the design and/or analysis?	Was the follow-up of patients complete?	How precise (for example, in terms of CI and p values) are the results?
Balkan C et al. 2010[12]	Y	–	Y	–	–	Y	–
Danielson H et al. 2017[24]	Y	–	Unclear	–	–	Y	–
Habermann B et al. 2004[23]	Unclear	–	N	–	–	Y	–
Holmstrom M et al. 2012[22]	Unclear	–	Y	–	–	Y	–
Ingerslev J et al. 1996[49]	Unclear	–	N	–	–	Y	–
Kraut EH et al. 2007[14]	N	–	N	–	–	Y	–
Lauroua P et al. 2009[54]	Y	–	Y	–	–	Y	–
Mauser-Bunschoten EP et al. 1998[16]	Unclear	–	N	–	–	Y	–
Mauser-Bunschoten EP et al. 2002[17]	Y	–	N	–	–	Y	–
Negrier C et al. 2013[93]	Y	–	Y	–	–	Y	–

Study	Was the cohort recruited in an acceptable way?	Was the exposure accurately measured to minimise bias?	Was the outcome accurately measured to minimise bias?	Have the authors identified all important confounding factors?	Have the authors taken account of the confounding factors in the design and/or analysis?	Was the follow-up of patients complete?	How precise (for example, in terms of CI and p values) are the results?
Quintana-Molina M et al. 2004[65]	Y	–	Y	–	–	Y	–
Serban M et al. 2014[21]	Y	–	Y	–	–	Y	Unclear
Smith OP et al. 2002[75]	Y	–	Unclear	–	–	Unclear	–
Tjonnfjord GE. 2004, 2006 [100, 101]	Y	–	Unclear	–	–	Y	–

Y: Yes; N: No

We are submitting the full manuscript as requested.